The extension of contact tracing over the whole country would undoubtedly be of benefit. It would make possible the follow up of those who move frequently and who may be named more than once under Regulation 33B without this repetition being discovered as the Forms may go to different medical officers of health according to where the contact is met. Information is sometimes obtained by the workers which could be used by contact tracers in other areas. It is the mobile contact who is not only most difficult to find but also probably the greatest danger to public health. Under a national scheme provision could be made for the sending of reports to the clinic from which the notification came so that if further action is necessary to find the source of infection, it can be taken.

Further information upon any aspect of the Tyneside Contact Tracing Scheme will be given willingly to any public or voluntary social service organisation on application being made to the

Liaison Officer, Miss H. M. JOHNS, M.A.,
The White House,
Grainger Park Road,
Newcastle upon Tyne, 4,

or to the Medical Officer of Health of any of the authorities participating in the Scheme ; namely,
The County Councils of Durham and Northumberland,
The County Borough Councils of Gateshead, Newcastle upon Tyne, Tynemouth and South Shields.

"MIDDLE EAST GRANULOMA": IS IT GRANULOMA VENEREUM?

By W. R. SCOTT COWE, M.B., Ch.B.
Captain, Royal Army Medical Corps ; Graded Venereologist, Middle East Forces

In the course of three years' work in venereal diseases treatment centres in the Middle East, I and my colleagues have come across many and varied types of penile ulceration which have received but scanty attention in the literature. These may be described as usually being infected abrasions in contrast with the proved syphilitic chancre or with chancroid. One group, however, which presents uniformly well defined characteristics, has come to our notice recently. We believe the condition to be a clinical entity and to be caused by a specific organism or virus. We had seen an occasional sore of this type in the past, but during the last six months we have had approximately 30 of these cases (picked out from among 350 other venereal sores) all from the same district and all presenting the same clinical features.

At first we believed on clinical grounds that we were dealing with a new type of venereal sore or possibly a marked modification of one which had already been described. However, after further examination of direct smears and micro-sections and the discovery of similar lesions in two prostitutes from this district, we have become fairly sure that we are dealing with early granuloma venereum (ulcerative granuloma ; granuloma inguinale).

It should be emphasized here that all penile lesions treated by us are considered to be syphilitic until proved to be otherwise by our finding that repeated dark-ground examination is negative for *Treponema pallidum* (*Spirochaeta pallida*) and that the Kahn test or the Wassermann reaction remains negative after three months' surveillance. We have thought that a description of this venereal sore and of our investigations, with a short discussion of our present findings, would be of some interest to those whose work leads them into the study of the many diversities of venereal infection.

Clinical aspects

The patients who present this lesion have almost without exception been exposed to infection in one particular district, such as a seaport. An occasional case has turned up from some other area but this again has been a seaport town. In addition exposure to infection has always been through intercourse with non-European women. The incubation period varies from one to four weeks, but usually by the fourth week after exposure the sore presents the typical appearances which we have come to recognize so well. At this stage the ulcer is well defined,

on the average about half-an-inch in diameter, with marked induration of its base and surrounding tissue. The edges are raised, more so in the spreading part, and from dark red to purple in colour. The ulcer extends into the corium with a fair amount of tissue destruction and its base shows a considerable tendency to bleed. The base itself frequently has the dull red appearance which is so often associated with a syphilitic sore, although in other cases, when secondary infection occurs, the base is covered with a greyish-yellow slough. In fact in the early stages, before the edges become heaped up, the appearance is very suggestive of syphilis. Repeated dark-ground examinations have, however, in every case failed to reveal *Treponema pallidum* and surveillance of these cases has shown negative Kahn and Wassermann reactions after three or four months. In contrast also to the text-book description of chancroid, the edges are regular and well defined without undermining. More important, microscopic examinations of smears and of cultures have failed to identify Ducrey's bacillus. Not long ago we obtained supplies of Ducrey vaccine for intradermal tests, but the few cases which we were able to test were all negative.

Typical features.—The usual sites for the ulcer in order of frequency are : (1) the inner aspects of the prepuce adjoining the coronal sulcus ; (2) the preputial edge in cases with partial phimosis. Typical ulcers have been observed occasionally on the fraenum and one ulcer was intrameatal. Two of the most recent cases showed extensive lesions in the groin as well as a sub-preputial ulcer. These were actually skin lesions and not suppurating buboes. The penile lesion is usually single but on occasion multiple ulcers occur on the edge of the prepuce.

In a typical case the history is of exposure to infection about three weeks before the appearance of the sore. (On two occasions there was the history of a small papule a few days after exposure which disappeared within a few days, the typical ulcer appearing in the same spot some four weeks later.)

On examination a well defined ulcer with the appearance described above is found to be present in the coronal sulcus, extending posteriorly along the preputial reflexion. The ulcer spreads slowly posteriorly for approximately three weeks, no matter what local treatment is used. It then becomes what we call " static". Infection of the base then subsides within from seven to ten days and the ulcer fills in slowly, healing taking place within a further ten days. When the ulcer is healed it leaves a recognizably fibrotic area. These three phases—progressive, static and healing—are well defined and it will be noted that at least six weeks' in-patient treatment in hospital is necessary, in contrast with the syphilitic or the soft sore, either of which clears up under treatment within ten to fourteen days at the most unless there is gross secondary infection.

Other characteristics.—Two other important features remain to be mentioned. First, the ulcer is absolutely painless despite the tissue destruction ; secondly, in two cases only was there any associated inguinal adenitis. The sores in both these cases, however, were very heavily infected and in addition the patients gave a previous history of an evanescent sub-preputial vesicle, so that the possibility of co-existent lymphogranuloma inguinale (lymphopathia venereum) could not be ruled out. Frei antigen was unfortunately not available at this time. The two recent cases with inguinal skin lesions are mentioned above. These showed no notable glandular involvement.

As is mentioned above, all these cases occurred after exposure to infection by non-European women, but the race incidence, as far as the male cases were concerned, was divided equally between European and non-European troops, although it was noticed that the ulceration was more extensive in the latter patients.

Bacteriology

Early investigations were on bacteriological lines. Although at first we suspected an atypical syphilitic sore, repeated dark-ground examinations were negative for *Treponema pallidum.* Occasionally a motile bacillus was seen. Smears were taken from the spreading edge of the ulcer, direct and by needle puncture, and stained by Gram's and Giemsa's methods. A few showed groups of Gram

positive cocci (probably staphylococci). Many showed Gram negative bacilli in moderate numbers and occasional diphtheroid bacilli. Apart from this, however, the most constant finding was an organism which resembled morphologically Friedländer's bacillus (*Klebsiella pneumoniae*). It was possible, in fact, to demonstrate a capsule by means of Hiss's stain in several of the specimens. Organisms resembling the Ducrey's bacillus were not seen. Culture methods are unfortunately rather difficult under Service conditions in the Middle East and all efforts were at first unsuccessful. In a more recent case, however, an organism which resembled morphologically *Micrococcus catarrhalis* was isolated in pure culture. This organism did not ferment any of the available sugars.

At first we had a theory that we might possibly be dealing with a transferred respiratory infection, largely in view of the fact that the majority of the prostitutes from the area in question use saliva as a lubricant. This suggestion, in combination with the finding of the Klebsiella-like organism which is known to occur also in certain nasal granuloma in non-Europeans, seemed at least plausible; it was discarded later after further study.

All the granuloma patients on discharge from hospital were placed under special surveillance; reports so far received on ex-patients who have completed their blood tests have shown negative Kahn and Wassermann reactions after three and four months.

Other bacteriological investigations

(1) Seven cases were tested with Frei antigen, all with negative results. Unfortunately supplies of this antigen have become available only lately. Clinically, however, the condition in no way resembles lymphogranuloma inguinale.

(2) All East African soldiers had blood slides examined for the presence of filaria (day and night). Again all the tests gave negative results despite the fact that a great number of these men suffer from filariasis and its consequent genital lesions.

Difficulties in diagnosis

It will be noted that the sore described did not conform in detail to any one of the common types which are generally found in fresh venereal infections. We were dealing therefore with either a new infection or a modification of one which had been already described. Regarding the latter hypothesis, the possibility of granuloma venereum was always kept in mind, particularly in view of the early finding of the Klebsiella-like organism (as originally described by Donovan) in direct smears from many of these cases. Quite frankly, however, at that time we had the impression that granuloma venereum was a much more extensive and destructive lesion than the comparatively small ulcer with which we were dealing and, in addition, that this disease was considered to be a rarity in the Middle East.

Treatment

Apart from the clinical interest of this condition we had also a natural anxiety regarding its treatment. Our initial efforts, which were purely empirical, were singularly unavailing. Most of the early cases were in-patients of the hospital for no less than six weeks and in some there were recurrences shortly after discharge. In the early stages of our investigations treatment was as follows: local saline dressings while dark-ground examinations were being carried out and later soaks with hypertonic saline solution or saturated solution of sodium sulphate. Apart from some cleansing action these had no effect on the ulcer, which progressed slowly. After the static phase, however, application of lotio rubra (zinc sulphate with lavender in water) or of a sulphonamide powder hastened the healing to some extent.

The first cases which we encountered were given a course of 24 grammes of sulphanilamide, sulphapyridine or sulphathiazole in six days. This at first tended to clear up any local secondary infection, but on cessation of the course the progress of the ulcer occasionally continued longer than usual and with more pus formation.

A very marked improvement was shown in the later cases, however, when sulphanilamide was given towards the end of the progressive phase, that is after two weeks in hospital. Infection cleared up and healing took place rapidly, the static phase being almost non-existent. The total stay in hospital of these cases was about four weeks. We came to the conclusion at this stage that, whereas the sulphonamide group of compounds was effective in clearing local infection, a certain local or general immunity to the causative organism had to be built up before the medicament would shorten materially the course of the disease. This again contrasts with the other types of venereal sore in which the initial administration of sulphonamides is very effective in shortening the course of the sore.

Histopathology

Added to the initial difficulties described was the lack of available literature on the subject. Consequently, with the new clinical entity in mind, together with the fact that all tests for other venereal ulcers were so far negative, it was decided to investigate the histopathology of the ulcer. The following is the report on two sections of tissue from a typical ulcer by Captain Morgan, R.A.M.C. (Central Pathological Laboratory, 4th October 1943).

> "Both sores show the same changes microscopically. Each is a shallow ulcer with a floor formed of granulation tissue. Small pegs of acanthotic epidermis are noted at the periphery of the ulcer. Below the floor for a depth of about one-sixth of an inch is a densely cellular granulomatous mass, the cells being chiefly lymphocytes with a general admixture of plasma cells. Endarteritis and periarteritis while not conspicuous are present. Staining of the sections by Gram and Ziehl-Neelson [methods] failed to reveal the presence of organisms. Levaditi preparations do not show any spirochaetes. Otherwise the appearances are not readily distinguishable from a hard chancre and had the history of these cases not been known one would almost certainly have diagnosed syphilis."

The evidence of this report, our consistently negative findings regarding other types of venereal sore and the receipt of negative blood test reports on our first cases under surveillance made us sure that we were dealing with an infective granuloma. Once again, however, it must be emphasized that we had not forgotten the possibility of late incubation of syphilis, which is not uncommon in the Middle East; in some cases on record it is as much as eighty days.

Further investigations

The following more recent investigations were then carried out.

Culture.—Repeated cultures from the spreading edge again gave negative results in all but one case, in which the diplococcus mentioned above was isolated.

Guinea-pig inoculations.—Inoculations made both directly from the ulcer and from the one successful culture each gave rise to a small traumatic sterile ulcer which healed spontaneously in four days. It in no way resembled the original sore.

Auto-inoculation.—In one of our typical cases which presented a sore in the coronal sulcus, a sterilized area on the thigh was scratched and inoculated by direct contact with the sore. In four days a small pustule developed and a smear from the pus showed the Gram negative intracellular diplococcal forms which we had found in most of our original cases. A week later this pustule had broken down to become a well defined ulcer with raised edges and indurated base, conforming in type to the ulcer described above. It healed coincidentally with the primary lesion, after treatment with sulphanilamide, at the end of the progressive stage.

Literature

At this point we were fortunate enough to obtain some literature on the subject of granulomata. Stitt, describing granuloma venereum, makes the following observation: "In scrapings from ulceration of the external genitalia Donovan reported finding macrophages containing numerous small bacilli—*Klebsiella granulomatis*. These are Gram negative encapsulated oval diplococcoid organisms, 1·5 by 2 micromillimetres. They resemble the Freidländer bacillus. These organisms are almost constantly present but may be secondary invaders."

This description certainly tallied with that of the organism which we had already noted and microphotographs resembled closely the appearance seen in our smears.

Brigadier Robert Lees, Consultant Venereologist, M.E.F., on a previous visit to the Centre had shown great interest in this new clinical entity and given much

helpful advice; we were grateful to receive from him Supplement No. 19 to *Venereal Diseases Information* of the United States Public Health Service. Greenblatt in this treatise gives an excellent detailed clinical and pathological description of granuloma venereum, which is summarized below. After careful perusal of this article and the examination of his photographs and microphotographs, we came to the conclusion that the diagnosis of granuloma venereum would fit the cases which we had been studying.

Granuloma venereum.—This is defined by Greenblatt as a granuloma of the external genitalia. It is a mildly contagious chronic progressive auto-inoculable disease which involves skin and corium. The aetiological factor is the Donovan body, probably a protozoon. Inoculation of animals with this organism has failed to reproduce the disease. It has been suggested that the Donovan body may be not a primary but a secondary invader, but once established it dominates the picture. A certain racial immunity has been noted in that proved granulomatous lesions in white people are occasionally self-limiting and heal spontaneously. The geographical distribution is now believed to be general as the clinical entity is becoming more readily recognized. Clinically the primary lesion is a well defined slowly progressive ulcer with characteristic rolled edges, in the advancing part the granulation tissue "piling over on to the bordering epithelial surface". It is painless and bleeds easily.

Three types are described: (1) exuberant, (2) ulcerative, (3) cicatrical. A pseudo-bubo may occur, the regional lymph nodes being only mildly infected or not at all. The histopathology shows the following features: (a) massive cellular reaction—luxuriant granulation tissue surcharged with plasma cells; (b) relative and conspicuous paucity of lymphocytes; (c) diffuse sprinkling of polymorphs with focal collection in superficies and papillae; (d) pronounced marginal epithelial proliferation simulating epitheliomatous changes; (e) pathognomonic large mononuclear cells scattered in varying numbers throughout the granulation tissue. This cell is from 25-90 micromillimetres in diameter and has many intraplasmic cysts filled with deeply stained bodies. Donovan bodies are round or rod-like, are grouped within the cysts and have an affinity for haematoxylin.

The diagnosis rests on the demonstration of the Donovan bodies and the pathognomonic large cell in direct smears and on biopsy. The mature forms are encapsulated. Coccoid, diplococcoid or bacilliform organisms are often present in smears; they are surrounded by a distinct halo lying within cystic spaces in the monocytes; these are suggestive of the immature forms.

Present investigations

With this evidence before us we began a renewed search of smears and biopsy sections. When an occasional fresh case showed the clinical entity, smears were taken and stained with haematoxylin and eosin. As before the majority contained the scattered diplococcal organisms which we had already noted, but now in a fair proportion of smears we were able to identify an occasional large mononuclear cell with visible cystic spaces.

Certain of the cells seen in section also corresponded very closely to Greenblatt's description of the pathognomonic cells. It was impossible, however, to be dogmatic about something which we had never seen before. At best all we could say was that there was a remarkable resemblance between our smears and sections and those described in the literature. Further expert pathological opinion was sought and now smears and sections are in the hands of a civilian pathologist, an expert in tropical diseases, who after several weeks of study has not yet committed himself to a definite diagnosis, although he agrees that the lesion is an infective granuloma.

Examination of prostitutes.—Not long ago, by arrangement with the civil authorities, we were present at the clinical examination of some twenty prostitutes from the area from which our granuloma patients had come. Of the cases examined, two were of considerable interest. Both were non-European. One showed considerable paravulvar nodular thickening extending upwards to the groin and the woman gave a previous history of recent extensive ulceration in that area. The other presented a well defined granulomatous ulcer with raised edges in the region of the fourchette, which had been present for many weeks. It bled easily and was painless. There was no concomitant sign of syphilis and the Wassermann reaction at this time was negative. A section was taken from this lesion and it is now in the hands of the civilian pathologist mentioned above.

Discussion

A penile sore has been described, which presents certain uniform features and a well defined clinical course. It is almost certainly of venereal origin, as every patient admits exposure to infection a short time before the appearance of the sore. It has been proved to be non-syphilitic and does not conform clinically or by laboratory tests to lymphogranuloma inguinale or to chancroid. Clinically it resembles granuloma venereum and tallies with the main points in the description given by Greenblatt.

Furthermore, the frequent presence of the diplococcal organisms in direct smears is highly suggestive of the mature Donovan bodies and, in addition, we believe that in several of the smears and sections the pathognomonic cell is present. (Unfortunately we are not ourselves expert pathologists.) The sore has been proved also to be auto-inoculable and to be nontransmissible to animals. If it is granuloma venereum the lesion is an early one and its small extent may possibly be ascribed to one or both of the two following factors.

(1) The postulated racial immunity. It has already been noted that the lesions tended to be more extensive in non-Europeans and were in addition rather more troublesome to cure ; furthermore the two cases in which inguinal ulceration occurred were of non-European patients.

(2) The military law imposes severe penalties for the concealment of venereal disease and encourages men to seek medical advice as soon as a lesion is discovered. It is noted that in civilian life patients often do not seek advice until a lesion becomes extensive, just because they do not suffer any pain or discomfort.

In pathological sections, however, the findings are as yet not conclusive. The appearances are simply those of an infective granuloma. There would seem also to be a preponderance of lymphocytes in contrast to the histological features described in the literature. We still await the result of expert study, and opinion must therefore be very guarded. Future investigations must be along the lines of repeated smears and sections taken from cases which show the clinical entity.

If the concensus of expert pathological opinion is against granuloma venereum, then a new granuloma of venereal origin, aetiology at present unknown, has been described, and this closely simulates a milder type of the former disease. The possibility of a virus infection must be borne in mind.

In regard to treatment, the peculiar response to the sulphonamide group has been mentioned and our practice now is to concentrate on local cleansing of the ulcer for the first two weeks and follow this with a 24-gramme course of sulphanilamide spread over 6 days. Most cases on this routine clear up in approximately one month. Heavy metals have been used with success in the treatment of the proved granulomata, but it would be obviously unwise to use such treatment in these cases until every one had been proved to be non-syphilitic.

One final and very important point remains to be mentioned. In all the granulomata the healing of the primary lesion does not by any means indicate the cure of the disease. We cite as examples syphilis, lymphogranuloma inguinale (lymphopathia venereum) and tuberculosis, all of which are generalized diseases. Thus it may be possible that the primary lesion which we have described is merely an initial indication of a generalized infection which will show future signs, or that it may remain infective despite the apparent cure.

Further study of aetiology and pathology is therefore imperative, particularly as many of our cases have occurred among British soldiers, who, we hope, will be coming home at no very distant date.

Summary

The clinical aspects of an unusual venereal sore which occurs in certain areas in the Middle East are described. Its bacteriology and pathology are discussed together with a successful method of treatment. The sore is an infective granuloma which resembles granuloma venereum in many of its aspects. It may possibly be a " new " venereal disease.

Findings are still inconclusive and nothing is as yet known about possible

after-effects in later life. The investigations are being continued and it is proposed in the near future to send sections to the London School of Tropical Medicine.

I wish to tender my very grateful thanks to Major F. L. Lydon, R.A.M.C., Specialist in Venereology, Officer Commanding this Centre, without whose help and kindly criticism this paper would have been impossible; to Captain Morgan, R.A.M.C., of the Central Pathological Laboratory, Middle East Forces, for his opinion on pathological specimens; to Major Davison, R.A.M.C., and Captain Caplin, R.A.M.C., Pathologists, for assistance in laboratory work; also to the staff of the Centre who have borne my demands for extra work with commendable patience.

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CLINICAL RECORDS

A FATAL CASE OF PURPURA HAEMORRHAGICA WITH AGRANULOCYTIC ANGINA AFTER ARSPHENAMINE THERAPY

The occurrence of blood dyscrasia after antisyphilitic treatment with compounds of the arsphenamine group is an uncommon complication but one which is often of grave import. These dyscrasias are usually classified into three main types: (1) thrombocytopenic purpura, (2) granulocytopenia and (3) aplastic anaemia. Although the literature on this subject is far from voluminous, reports of instances of each of these main types are readily found. Occasional reports suggest that cases cannot always be readily classified in any one of these three groups.

The following case, which showed the characteristics of both type 1 and type 2, exhibited marked purpuric haemorrhages, together with the rare complication of haematuria, and granulocytopenia with severe faucial ulceration, which proved fatal, also developed.

Case report

On December 3rd 1940 a married woman, aged 27 years, was transferred to this clinic bearing documents (Booklet V15) which indicated that she had commenced treatment for secondary syphilis and had received, one week earlier, 0·06 gramme of mapharsen and 0·4 gramme of bismuth. Her general condition was good, with weight 7 st. 13 lb. A fading rash was still perceptible. The heart was normal. The urine did not contain any albumin.

During the period from 3rd December 1940 to 11th February 1941 she received a total of 4 grammes of stabilarsan (arsphenamine and glucose) and 1·4 grammes of bismuth. She showed no sign of intolerance and made a slight gain in weight. On 18th February potassium iodide was prescribed, but to this drug intolerance was shown by the occurrence of a rash and of swollen glands. These signs quickly disappeared when the drug was omitted. She was given 0·45 gramme of stabilarsan on 14th March and on her next attendance on 25th March a papular rash was evident on her back and legs. She was therefore treated with six injections of 0·6 gramme of calciostab (calcium thiosulphate) during the next fourteen days, and by 15th April the rash had disappeared and she appeared to be well. The blood Wassermann reaction, which had been strongly positive on her first attendance, was still strongly positive on this date.

When she attended on 22nd April she was found to have slight oedema of both feet. The urine contained a few pus cells and a trace of albumin but renal casts were absent. The heart appeared to be normal and there were no obvious varicose veins. The oedema had disappeared by 13th May. On 10th June the blood Wassermann reaction was found to be negative.

In view of these signs of intolerance and of the negative Wassermann reaction at this time, she was kept under surveillance up to March 1942, when she was found to be 6 months pregnant. The Wassermann reaction was still negative but, on account of the pregnancy, treatment with 3 grammes of quinostab (quinine iodobismuthate suspended in olive oil) was given from 24th March to 6th May. A healthy child was born on 25th June.

On 3rd August the Wasserman gave a doubtful result, but this was positive on 28th August after a provocative injection of 0·3 gramme of neoarsphenamine. She made no further attendance until October, when the provocative Wassermann result was again positive. There were no signs of clinical relapse. She had an illness which was reported as "influenza" shortly afterwards and was away from the clinic until 4th January 1944. On this occasion treatment with potassium iodide was well tolerated. On 10th February, as the blood